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PERSPECTIVE

Focus on Receptors for Coronaviruses with Special Reference to Angiotensin-Converting Enzyme 2 as a Potential Drug Target - A Perspective

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Coronaviruses (CoVs) possess an enveloped, single, positive-stranded RNA genome that encodes for four membrane proteins, namely spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins 3-5 [1]. With regard to pathogenicity, S proteins are essential for viral entry into host cells [2, 3]. SARS-CoV binds to the angiotensin-converting enzyme (ACE)2, which is present on non-immune cells, such as respiratory and intestinal epithelial cells, endothelial cells, kidney cells (renal tubules) and cerebral neurons and immune cells, such as alveolar monocytes/macrophages [4-6]. Of note, CD209L or liver/lymph node special intercellular adhesion molecule-3-grabbing non-integrin (SIGN) and dendritic cell (DC)-SIGN are alternative receptors for SARS-CoV but with lower affinity [7]. In the case of MERS-CoV, S proteins bind to the host cell receptor dipeptidyl peptidase 4 (DPP4 or CD26), which is broadly expressed on intestinal, alveolar, renal, hepatic and prostate cells as well as on activated leukocytes [8]. Then, viruses replicate in target cells with the release of mature virions, which, in turn, invade new target cells [9]. Evidence has been provided that SARS-CoV proteins are cleaved into two subunits, S1 and S2, respectively, and the amino acids 318-510 of the S1 represent the receptor-binding domain (RBD) which binds to ACE2 [10, 11]. Quite importantly, in the context of RBD, there is the receptor-binding motif (RBM) (amino acids 424-494), which accounts for complete binding to ACE2 [11]. Moreover, by means of two residues at positions 479 and 487, RBD allows virus progression and tropism [10, 11]. In the case of MERS-CoV, its RBM binds to DPP4 with residues 484-567, thus, suggesting that its RBD differs from that of SARS-CoV [12, 13]. In a very recent paper, Wan and associates [14] investigated the receptor recognition by COVID-19 (a new term to indicate the 2019-nCoV in Wuhan) on the basis of structural studies. In this respect, the sequence of COVID-19 RBM is similar to that of SARS-CoV, thus implicating that ACE2 may represent the binding receptors for COVID-19. Furthermore, gln493 residue of COVID-19 RBM seems to allow interaction with human ACE2, thus, suggesting the ability of this virus to infect human cells. According to the structural analysis by Wan and associates [14], COVID-19 binds to human ACE2 with lesser efficiency than human SARS-CoV (2002) but with higher affinity than human SARS-CoV (2003). Furthermore, the same authors predicted that a single mutation at the 501 position may enhance the COVID-19 RBD binding capacity to human ACE2 and this evolution should be monitored in infected patients [14]. These predictive findings by Wan and associates [14] are confirmed by two contemporary studies by Letko and Muster [15] and Peng and associates [16]. In particular, the report by Peng and associates [16] points out the possible origin of COVID-19 from bats [16].

From a pathogenic point of view, evidence has been provided that binding of S2 to the ACE2 receptor leads to its down-regulation with subsequent lung damage in the course of SARS-CoV infection [17]. Down-regulation of ACE2 causes excessive production of angiotensin (ANG) II by the related enzyme ACE with the stimulation of ANG type 1a receptor (AT1R) and enhanced lung vascular permeability [18]. In particular, the same authors have reported that recombinant ACE2 could attenuate severe acute lung injury in mice [18]. Moreover, Battle and associates [19] also proposed to use the already available recombinant ACE2 for intercepting COVID-19 and attenuating infection.

In the previous paragraphs, the presence of ACE2 on immune cells has been pointed out and, by analogy to epithelial cells, this receptor may also be down-regulated following viral entry. Therefore, in CoV-infected animal models and in infected humans, further investigations are required to clarify a possible reduced expression of ACE2 on immune cells. In fact, in the course of SARS-CoV infection, a number of immune disorders have been detected. Three reports have demonstrated the ability of CoV to inhibit interferon (IFN)-β production in the course of SARS acting as an IFN antagonist [20-22]. In senescent Balb/c mice, depletion of T lymphocytes is associated with more severe interstitial pneumonitis and delayed clearance of SARS-CoV, thus, suggesting a protective role played by these cells [23]. In this connection, both SARS-CoV and MERS-CoV have been shown to induce T cell apoptosis, thus, aggravating the clinical course of disease [24, 25]. Quite interestingly, memory $CD8^+$ T cells specific for SARS-CoV M and N proteins have been detected up to 11 years post-infection [26]. As far as humoral

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immune responsiveness is concerned, evidence has been provided that the S1 subunit from MERS-CoV is highly immunogenic in mice [27]. Moreover, monoclonal antibodies have been shown to be highly neutralizing against MERS-CoV replication and endowed with post-exposure effectiveness in susceptible mice [28, 29]. Human neutralizing antibodies have also been isolated from a recovered patient, thus, suggesting the role of humoral immunity in the control of the persistence of CoV in the host [30]. In particular, IgG response occurs early in infection and its prolonged production may serve for virus clearance during recovery, also in view of the absence of viremia in convalescent sera from SARS patients [31].

According to current literature, the severity of COVID-19 infection correlates with lymphopenia and patients who died from COVID-19 had lower lymphocyte counts when compared to survivors [32, 33]. These data suggest that lymphocyte-mediated anti-viral activity is poorly effective against COVID-19. Despite lymphopenia, evidence for an exaggerated release of proinflammatory cytokines [interleukin (IL)-1 and IL-6] has been reported in the course acute respiratory syndrome in COVID-19 infected patients, thus, aggravating the clinical course of the disease [34]. As recently reported, during the COVID-19 pandemic in both Italy and China, a higher number of fatalities have been observed in the frail elderly population with previous comorbidities [35]. It is well known that the decline of immunity occurs in ageing and, therefore, COVID-19 may gain easier access to the respiratory tract in frail elderly patients [36].

There is evidence that ACE2 protects from severe acute lung failure and operates as a negative regulator of the renin-angiotensin system (RAS) [18, 37]. It is well known that ANG II *via* activation of the AT1R promotes detrimental effects on the host, such as vasoconstriction, reactive oxygen species generation, inflammation and matrix remodelling [38]. ACE2 counterbalances the noxious effects exhibited by ANG II and AT1R *via* activation of AT2R, which arrests cell growth, inflammation and fibrosis [39]. In this framework, Gurwitz [40] proposed to use AT1R blockers, such as losartan, as a potential treatment of COVID-19 infection. In fact, losartan as well as olmesartan, used for treating hypertension in patients, were able to increase ACE2 expression after 28 days of treatment of rats with myocardial infarction [41]. Then, Gurwitz suggests to evaluate the severity of symptoms in COVID-19 infected patients under previous chronic treatment with AT1R blockers in comparison to COVID-19 infected patients who did not take AT1R blockers [40]. Quite interestingly, 75% of aged COVID-19 infected patients admitted to Italian hospitals had hypertension [unpublished data]. However, the putative effects of ACE-2 down-regulation on the cardiovascular system in the course of the COVID-19 pandemic need more intensive studies.

Taken together, these pieces of evidence suggest that CoV-induced down-regulation of ACE2 activates RAS with collateral damage to organs, such as lungs, in the course of SARS-related pneumonia. Then, putative therapeutic measures aimed at increasing ACE2 levels on respiratory epithelial cells should be taken into serious consideration. Quite interestingly, over the past few years, three key papers have demonstrated the ability of a polyphenol, resveratrol (RES), to experimentally deactivate the RAS system in maternal and post-weaning high-fat diet, arterial ageing and high-fat diet, respectively [42-44]. In all these experimental models, RES led to an increase of ACE2 with a reduction of organ damage, such as liver steatosis and aorta media thickness and a decrease of adipose tissue mass, respectively. As far as the mechanism of action of RES is concerned, this polyphenol is able to activate sirtuin (Sirt)1 [45-47]. In turn, Sirt1 down-regulates AT1R expression *via* ACE2 up-regulation [43, 48]. Of importance, Lin and associates [48] have demonstrated the ability of RES to *in vitro* inhibit MERS-CoV infection of Vero E6 cells, thus, prolonging cell survival in virtue of an anti-apoptotic mechanism. These findings suggest a direct antiviral effect exerted by RES. It would be very interesting to evaluate the direct effects of RES on COVID-19 *in vitro*.

The data above discussed strongly suggest that RES, as an activator of ACE2, should be investigated in animal models of CoV-induced severe pneumonia, also taking into account the anti-oxidant, anti-inflammatory and immunomodulating effects exerted by polyphenols [49]. Then, successful animal studies may pave the way for RES-based human trials in COVID-infected patients.

During the reviewing process of this perspective, other related papers have been published.

Hanff and associates [50] have discussed the possible association between COVID-19-associated cardiovascular mortality and dysregulation of the RAS. From a pharmacologic point of view, RAS inhibition leads to the upregulation of ACE2; thus, attenuating acute respiratory syndrome and myocarditis in COVID-19-infected patients. Conversely, an increase in ACE2 expression may facilitate access into the host of COVID-19, thus, aggravating the clinical picture. Such a dilemma would be solved by clinical trials based on RAS blockade or initiation and monitoring related effects. Contemporarily, Danser and associates [51] claim that there is no evidence to stop RAS blockers in the course of COVID-19 infection. In fact, there are no available data that support the finding that ACE inhibitors or ANG II type I receptor blockers increase COVID-19 infection *via* its binding to ACE2. Finally, Kuster and associates [52] wrote that there are no data on the strict relationship between ACE2 activity and SARS-CoV2 mortality. Moreover, in the SARS-CoV2, cells expressing ACE2 were not attacked by the virus, while cells lacking ACE2 were bound by the SARS-CoV2 virus [53].

These findings suggest that also in the case of RES effects on COVID-19 infection, the dual role of ACE2 should be taken into serious consideration.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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